II. REMARKS

Formal Matters

Claims 1-18 are pending after entry of the amendments set forth herein.

Claims 1-9 were examined and were rejected. Claims 10-14 were withdrawn from consideration.

Claims 1, 5, and 6 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claim 6 is found in claim 3 as originally filed. Support for the amendments to claims 1 and 5 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: claim 1: paragraphs 0008, 0030, and 0047; and claim 5: paragraphs 0058 and 0059. Accordingly, no new matter is added by these amendments.

Claims 15-18 are added. Support for new claims 15-18 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claim 15: paragraph 0034; claim 16: paragraphs 0035 and 0036; claim 17: paragraphs 0021, 0038, and 0043; claim 18: paragraph 0046. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Restriction requirement

The Office Action set out a restriction requirement as follows:

Group I: claims 1-9; and

Group II: claims 10-14.

A provisional election of Group I (claims 1-9) was made telephonically, without traverse. Applicants hereby affirm the election of Group I (claims 1-9) for prosecution on the merits.

Rejections under 35 U.S.C.§112, second paragraph

Claims 1-9 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

Claim 1

The Office Action stated that claim 1 is incomplete. The Office Action stated that: 1) it is not clear how merely contacting a sample with an α-dicarbonyl compound results in ADMA detection; 2) it

is not clear whether/how contacting a sample with an α-dicarbonyl compound is directly involved in detection; and 3) it is not clear what steps or structures are required for detecting ADMA in the sample, or whether there is a causal relationship between contacting a sample with an α-dicarbonyl compound and the step required for detecting ADMA in the sample. Applicants respectfully traverse the rejection.

The instant invention as claimed provides a method of detecting asymmetric dimethylarginine (ADMA) in a sample comprising ADMA, symmetric dimethylarginine (SDMA), and arginine. Previous methods of detecting ADMA in a sample suffered from the drawback that the methods did not readily distinguish between ADMA, SDMA, and arginine. Claim 1 recites that contacting a sample with an α-dicarbonyl compound, which sample is suspected of containing ADMA and at least one of SDMA and arginine, results in modification of guanidino nitrogens SDMA and the arginine, producing modified SDMA and modified arginine. Unlike SDMA and arginine, the modified SDMA and the modified arginine are readily distinguishable from ADMA. ADMA can then be detected by various methods, which distinguish ADMA from modified SDMA and modified arginine. Thus, claim 1 as written is clear, and need not be amended.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to recite "wherein said modified SDMA and said modified arginine are distinguishable from ADMA."

Claim 3

The Office Action stated that the recitation of "modified" is indefinite. The Office Action stated that it is not clear how the α-amino group of SDMA, ADMA, and arginine is modified, or what steps are required for modification. Applicants respectfully traverse the rejection.

The specification provides ample discussion of modification of the α-amino group of SDMA, ADMA, and arginine. Substitute Specification, paragraphs 0044-0046. The term "modified" is well understood in the art. Accordingly, claim 3 is clear and need not be amended.

Claim 5

The Office Action stated that the recitation of "contacting the sample with an antibody that binds specifically to dimethylarginines, wherein said antibody does not bind to the modified SDMA" is seemingly contradictory. The Office Action stated that it appears that "modified SDMA" is a dimethylarginine. Applicants respectfully traverse the rejection.

Modified SDMA as recited in claim 1 results from modification of the guanidino nitrogens with an α-dicarbonyl compound. The modified SDMA of claim 1 is not recognized and bound by antibody that binds (unmodified) SDMA and ADMA. Accordingly, claim 5 is clear and need not be amended.

Nevertheless, and solely in the interest of expediting prosecution, claim 5 is amended to recite "contacting the sample with an antibody that binds specifically to ADMA and SDMA."

Conclusion as to the rejections under 35 U.S.C.§112, second paragraph

Applicants submit that the rejections of claims 1-9 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§103(a)

Claims 1-8 were rejected under 35 U.S.C.§103(a) as allegedly unpatentable over Balint and Cooke (WO 98/49199; "Balint") in view of Duerksen and Wilkinson ((1987) *Anal. Biochem.* 160:444-454; "Duerksen").

The Office Action stated: 1) Balint teaches a method of detecting ADMA in a sample comprising ADMA, SDMA, and arginine, comprising the step of detecting ADMA; 2) Balint does not teach the step of contacting the sample with an α-dicarbonyl compound; 3) Duerksen teaches the use of an α-dicarbonyl compound (4-(oxoacetyl)phenoxyacetic acid; OAPA) as a linker for immobilizing arginine-containing compounds to solid phases. The Office Action concluded that it would have been obvious to modify the method of Balint of detecting ADMA with the use of OAPA. Applicants respectfully traverse the rejection.

Comments regarding the criteria to establish a *prima facie* case of obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). All three criteria must be met. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations.

Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint neither discloses nor suggests a method of detecting ADMA in a sample comprising ADMA, SDMA, and arginine, where the method involves contacting the sample with an α-dicarbonyl compound to modify the guanidino nitrogens of SDMA and arginine, where the modified SDMA and the modified arginine are distinguishable from ADMA.

Duerksen does not cure the deficiency of Balint. Duerksen discusses a method of activating polyacrylamide beads to bind proteins via arginine residues to the beads, using OAPA as a linking reagent. Duerksen reports that OAPA reacts with the arginine in the protein, and with aminated polyacrylamide beads, thereby coupling arginine-containing proteins to the beads. Duerksen, Abstract; and page 450, column 2; and page 452. Nowhere does Duerksen discuss contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations. Accordingly, Balint, alone or in combination with Duerksen, does not render claims 1-8 obvious.

There is no motivation or suggestion in the cited references to modify Balint or to combine the teachings of Balint and Duerksen.

As noted above, Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint discusses the problem of detecting ADMA in samples that include, in addition to ADMA, SDMA and arginine. Balint, page 7, lines 28-32. However, Balint does not propose any modifications of SDMA or arginine that would make these two compounds distinguishable from ADMA. Accordingly, there is no motivation in Balint to look to the teaching of Duerksen.

Duerksen does not provide any motivation to modify Balint, or to combine the teachings of Balint and Duerksen. As noted above, Duerksen discusses a method of activating polyacrylamide beads to bind proteins via arginine residues to the beads, using OAPA as a linking reagent. Nowhere does Duerksen discuss contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified

SDMA and the modified arginine are distinguishable from ADMA. Duerksen does not mention the problem of detecting ADMA in a sample that includes ADMA, SDMA, and arginine.

There is no reasonable expectation of success in the cited references.

As noted above, Balint discusses antibodies that are specific for ADMA, and detection methods using the antibodies. Balint discusses the problem of detecting ADMA in samples that include, in addition to ADMA, SDMA and arginine. Balint, page 7, lines 28-32. However, Balint does not propose any modifications of SDMA or arginine that would make these two compounds distinguishable from ADMA. As such, Balint does not provide any reasonable expectation of success of a method involving contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

Duerksen does not provide a reasonable expectation of success. Duerksen does not discuss a method involving contacting a sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, so as to modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA. There is no reasonable expectation of success in Duerksen that contacting sample suspected of containing ADMA and at least one of SDMA and arginine with an α-carbonyl compound, would modify SDMA and arginine, such that the modified SDMA and the modified arginine are distinguishable from ADMA.

Conclusion as to the rejection under 35 U.S.C.§103(a)

Balint, alone or in combination with Duerksen, does not teach or suggest all of the claim limitations; there is no motivation or suggestion in the cited references to modify Balint or to combine the teachings of Balint and Duerksen; and there is no reasonable expectation of success in the cited references. Accordingly, Balint, alone or in combination with Duerksen, cannot render claims 1-8 obvious.

Applicants submit that the rejection of claims 1-8 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-276.

Respectfully submitted,
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Date: June 8, 2005

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